```
=> d his ful

     (FILE 'HOME' ENTERED AT 10:33:18 ON 25 JUL 2005)

     FILE 'REGISTRY' ENTERED AT 10:33:23 ON 25 JUL 2005
                E MYCOPHENOLATE MOFETIL/CN
L1              1 SEA ABB=ON  PLU=ON  "MYCOPHENOLATE MOFETIL"/CN
                D SCA
                D
L2                STR 128794-94-5
L3              8 SEA FAM FUL L2
                D SCA
                E 2-MORPHOLINOETHANOL/CN
L4              1 SEA ABB=ON  PLU=ON  2-MORPHOLINOETHANOL/CN
                D
L5                STR 622-40-2
L6             59 SEA FAM FUL L5

     FILE 'CAPLUS' ENTERED AT 10:35:16 ON 25 JUL 2005
L7             14 SEA ABB=ON  PLU=ON  L3(L)PREP+ALL/RL
L8            588 SEA ABB=ON  PLU=ON  L6(L)RACT+ALL/RL
L9             11 SEA ABB=ON  PLU=ON  L7 AND L8

     FILE 'REGISTRY' ENTERED AT 10:36:23 ON 25 JUL 2005
                E METHYL MYCOPHENOLATE/CN
L10             1 SEA ABB=ON  PLU=ON  "METHYL MYCOPHENOLATE"/CN
                D SCA
                D
L11               STR 31858-66-9
L12            16 SEA SSS SAM L11
L13           235 SEA SSS FUL L11

     FILE 'CAPLUS' ENTERED AT 10:37:26 ON 25 JUL 2005
L14            39 SEA ABB=ON  PLU=ON  L13(L)RACT+ALL/RL
L15             3 SEA ABB=ON  PLU=ON  L14 AND L7
L16             2 SEA ABB=ON  PLU=ON  L15 AND L8
L17       1387200 SEA ABB=ON  PLU=ON  CAT/RL OR ?CATAL?
L18             5 SEA ABB=ON  PLU=ON  L7 AND L17
L19            14 SEA ABB=ON  PLU=ON  L7 OR L9 OR L15 OR L16 OR L18
                E US2003-750466/APPS
L20             1 SEA ABB=ON  PLU=ON  US2003-750466/AP
                SEL RN

     FILE 'REGISTRY' ENTERED AT 10:39:54 ON 25 JUL 2005
L21            13 SEA ABB=ON  PLU=ON  (108-88-3/BI OR 128794-94-5/BI OR 1330-20-7
                   /BI OR 141-78-6/BI OR 21651-19-4/BI OR 31858-66-9/BI OR
                   32483-51-5/BI OR 40336-78-5/BI OR 622-40-2/BI OR 71-43-2/BI OR
                   745067-13-4/BI OR 75-09-2/BI OR 818-08-6/BI)

     FILE 'CAPLUS' ENTERED AT 10:39:59 ON 25 JUL 2005
L22             1 SEA ABB=ON  PLU=ON  L20 AND L21
                D IALL HITSTR
L23             1 SEA ABB=ON  PLU=ON  L22 AND L19
                D QUE STAT L19

     FILE 'USPATFULL, USPAT2' ENTERED AT 10:41:46 ON 25 JUL 2005
L24             1 SEA ABB=ON  PLU=ON  L3 AND L6 AND L13

     FILE 'STNGUIDE' ENTERED AT 10:42:31 ON 25 JUL 2005
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FILE HOME

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 24 JUL 2005 HIGHEST RN 856767-39-0
DICTIONARY FILE UPDATES: 24 JUL 2005 HIGHEST RN 856767-39-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

FILE CAPLUS

FILE COVERS 1907 - 25 Jul 2005 VOL 143 ISS 5
FILE LAST UPDATED: 24 Jul 2005 (20050724/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 21 Jul 2005 (20050721/PD)
FILE LAST UPDATED: 21 Jul 2005 (20050721/ED)
HIGHEST GRANTED PATENT NUMBER: US6920641

HIGHEST APPLICATION PUBLICATION NUMBER: US2005160510
CA INDEXING IS CURRENT THROUGH 21 Jul 2005 (20050721/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 21 Jul 2005 (20050721/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 21 Jul 2005 (20050721/PD)
FILE LAST UPDATED: 21 Jul 2005 (20050721/ED)
HIGHEST GRANTED PATENT NUMBER: US2004197500
HIGHEST APPLICATION PUBLICATION NUMBER: US2005160493
CA INDEXING IS CURRENT THROUGH 21 Jul 2005 (20050721/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 21 Jul 2005 (20050721/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2005

USPAT2 is a companion file to USPATFULL. USPAT2 contains full text of the latest US publications, starting in 2001, for the inventions covered in USPATFULL. USPATFULL contains full text of the original published US patents from 1971 to date and the original applications from 2001. In addition, a USPATFULL record for an invention contains a complete list of publications that may be searched in standard search fields, e.g., /PN, /PK, etc.

USPATFULL and USPAT2 can be accessed and searched together through the new cluster USPATALL. Type FILE USPATALL to enter this cluster.

Use USPATALL when searching terms such as patent assignees, classifications, or claims, that may potentially change from the earliest to the latest publication.

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 22, 2005 (20050722/UP).

=> d que stat l19
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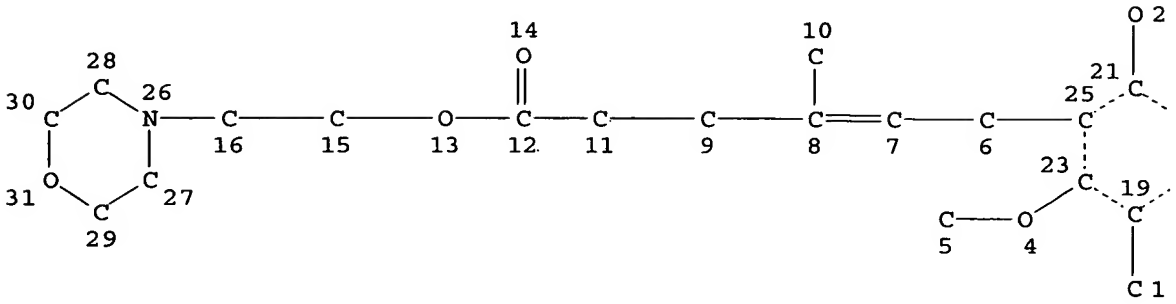

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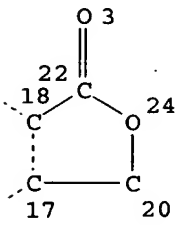

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 31

STEREO ATTRIBUTES: NONE
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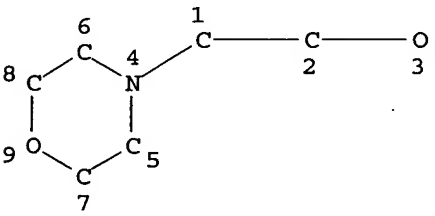
L5 STR



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DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS 9

STEREO ATTRIBUTES: NONE
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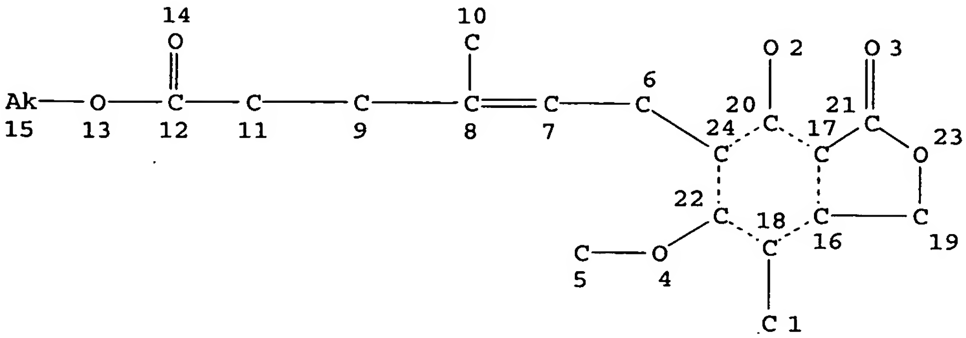
L8 588 SEA FILE=CAPLUS ABB=ON PLU=ON L6(L)RACT+ALL/RL
L9 11 SEA FILE=CAPLUS ABB=ON PLU=ON L7 AND L8
L11 STR



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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS 24

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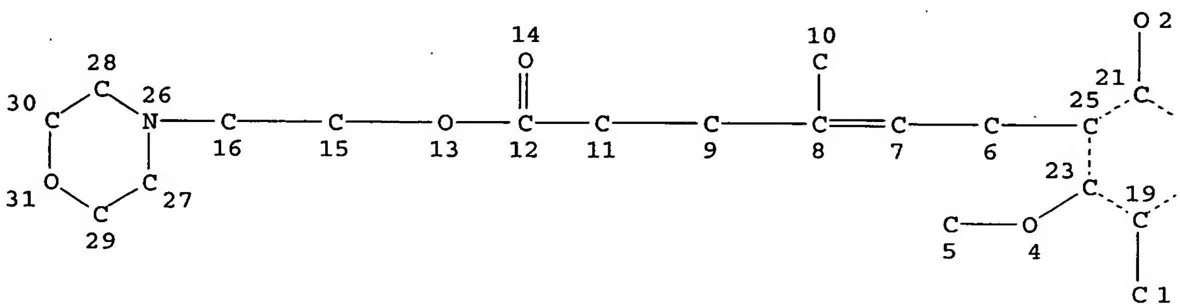
L16 2 SEA FILE=CAPLUS ABB=ON PLU=ON L15 AND L8
L17 1387200 SEA FILE=CAPLUS ABB=ON PLU=ON CAT/RL OR ?CATAL?
L18 5 SEA FILE=CAPLUS ABB=ON PLU=ON L7 AND L17
L19 14 SEA FILE=CAPLUS ABB=ON PLU=ON L7 OR L9 OR L15 OR L16 OR L18

=> d que stat l24
L2 STR



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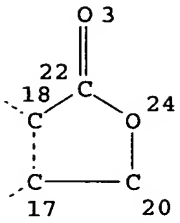

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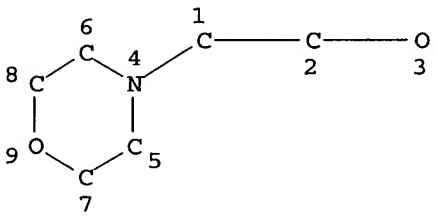

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STEREO ATTRIBUTES: NONE
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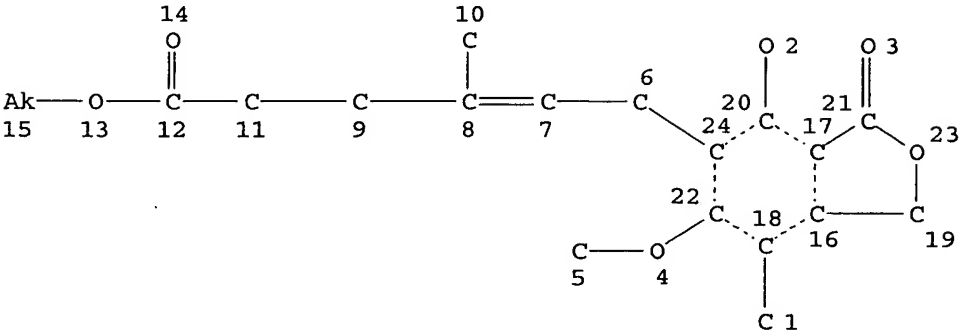

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NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE
L13 235 SEA FILE=REGISTRY SSS FUL L11
L24 1 SEA L3 AND L6 AND L13

=> d l19 ibib abs hitind hitstr 1-
YOU HAVE REQUESTED DATA FROM FILE 'CAPLUS' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 14 ANSWERS - CONTINUE? Y/(N):y

L19 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:238976 CAPLUS
DOCUMENT NUMBER: 142:297995
TITLE: Process for the production of mycophenolate mofetil
INVENTOR(S): Greil, Julia; Ludescher, Johannes; Wolf, Siegfried
PATENT ASSIGNEE(S): Sandoz A.-G., Switz.
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005023791	A2	20050317	WO 2004-EP10134	20040910

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
AT 2003-1433	A	20030911
AT 2003-2029	A	20031217
AT 2003-2030	A	20031217

AB The present invention relates to a new and economically attractive process for the production of mycophenolate mofetil in a high degree of pharmaceutically acceptable purity, which comprises the reaction of a reactive derivative of mycophenolic acid with 4-(2-hydroxyethyl)morpholine under acidic reaction conditions and the subsequent extraction of the pure mycophenolate mofetil through salt formation and release of the free base. A further aspect of the invention relates to the purification of mycophenolate mofetil by removing its byproducts, in particular its dimeric byproducts, by means of treatment with a primary or secondary amine. E.g., mycophenolic acid was dissolved at room temperature in a mixture of dichloromethane and N,N-dimethylformamide and the solution cooled to ca.

0°; a solution of oxalyl chloride in dichloromethane was added dropwise. A solution of 4-(2-hydroxyethyl)morpholine in dichloromethane was added dropwise. The solution was subsequently boiled under reflux for ca. 12 h, cooled, and mixed with water. The two-phase solution was stirred and the pH value adjusted to ca. 8.0 with saturated NaHCO3soln. The phases were separated and the aqueous phase extracted with dichloromethane. The combined organic phases were mixed with water and saturated NaHCO3 solution, the mixture stirred for ca. 20 min., and the phases separated N-butylamine was added. The dichloromethane phase was then extracted with water and HCl, the phases separated, and the organic phase washed with water and saturated NaHCO3 solution; the solution was mixed with activated carbon. Mycophenolate mofetil obtained after solvent evaporation contained undetectable dimers (HPLC).

IC ICM C07D307-88

CC 27-13 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 45

IT **116680-01-4P**, Mycophenolate mofetil hydrochloride
847904-42-1P
RL: **IMF (Industrial manufacture)**; RCT (Reactant); **SPN (Synthetic preparation)**; **PREP (Preparation)**; RACT (Reactant or reagent)
(production and purification of mycophenolate mofetil)

IT **128794-94-5P**, Mycophenolate mofetil
RL: **IMF (Industrial manufacture)**; **SPN (Synthetic preparation)**; **PREP (Preparation)**
(production and purification of mycophenolate mofetil)

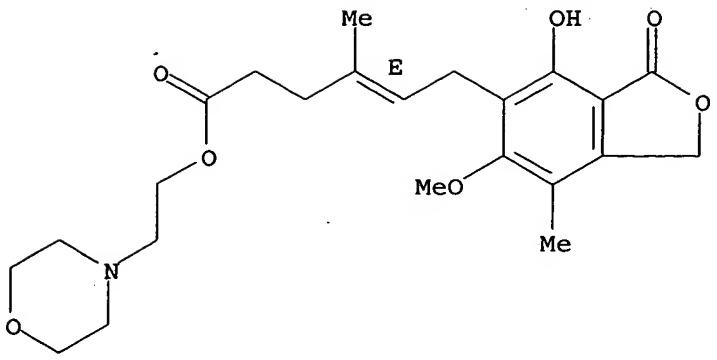
IT **622-40-2**, 4-(2-Hydroxyethyl)morpholine 24280-93-1, Mycophenolic acid
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(production and purification of mycophenolate mofetil)

IT **116680-01-4P**, Mycophenolate mofetil hydrochloride
847904-42-1P
RL: **IMF (Industrial manufacture)**; RCT (Reactant); **SPN (Synthetic preparation)**; **PREP (Preparation)**; RACT (Reactant or reagent)
(production and purification of mycophenolate mofetil)

RN 116680-01-4 CAPLUS

CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, hydrochloride, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



● HCl

RN 847904-42-1 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)-, ethanedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 128794-94-5
CMF C23 H31 N O7

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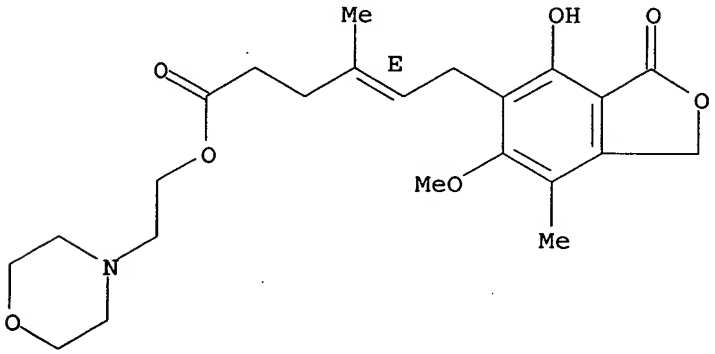
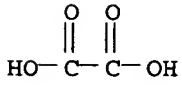


CM 2

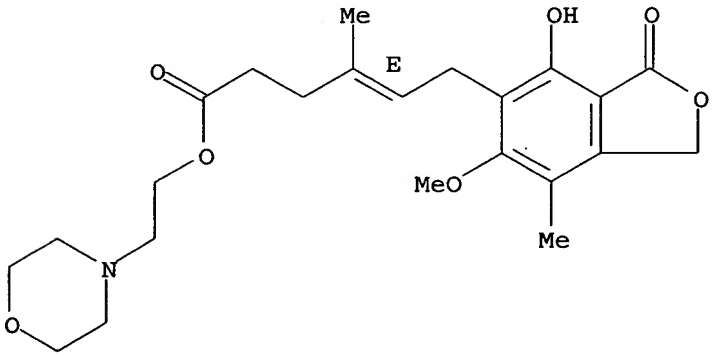
CRN 144-62-7
CMF C2 H2 O4



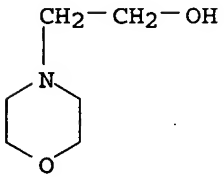
IT **128794-94-5P**, Mycophenolate mofetil

RL: **IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)**
(production and purification of mycophenolate mofetil)
RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **622-40-2**, 4-(2-Hydroxyethyl)morpholine
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(production and purification of mycophenolate mofetil)
RN 622-40-2 CAPLUS
CN 4-Morpholineethanol (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



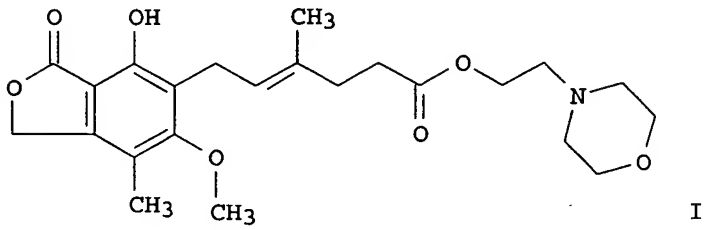
L19 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:878397 CAPLUS
DOCUMENT NUMBER: 141:366238
TITLE: Microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate
INVENTOR(S): Adhikary, Laxmi; Suryanarayan, Shrikumar
PATENT ASSIGNEE(S): Biocon Limited, India
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004089946	A1	20041021	WO 2003-IN143	20030407

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2003-IN143 20030407
OTHER SOURCE(S): CASREACT 141:366238
GI



I

AB 4-[(2-Hydroxyethyl)morpholino] mycophenolate I is prepared by the esterification of mycophenolic acid or its salts with 4-(2-hydroxyethyl)morpholine under microwave irradiation

IC ICM C07D413-12

CC 28-13 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 67

IT Esterification **catalysts**
(acids; microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate)

IT Acids, uses
RL: **CAT (Catalyst use)**; USES (Uses)
(esterification **catalysts**; in a microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate)

IT Clays, uses
RL: **CAT (Catalyst use)**; USES (Uses)
(montmorillonitic, support; microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate)

IT Bentonite, uses
Charcoal
Diatomite
Polymers, uses
Silica gel, uses
RL: **CAT (Catalyst use)**; USES (Uses)
(support; microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate)

IT 7440-44-0, Activated carbon, uses
RL: **CAT (Catalyst use)**; USES (Uses)
(activated, support; microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate)

IT 104-15-4, uses 7647-01-0, Hydrochloric acid, uses 7664-38-2, Phosphoric acid, uses 7664-93-9, Sulfuric acid, uses 7697-37-2, Nitric acid, uses
RL: **CAT (Catalyst use)**; USES (Uses)
(esterification **catalyst**; in a microwave esterification

synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate)

IT 75-75-2, Methanesulfonic acid 75-98-9, Pivalic acid 76-05-1, Trifluoroacetic acid, uses
RL: **CAT (Catalyst use)**; USES (Uses)
(esterification **catalyst**; microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate)

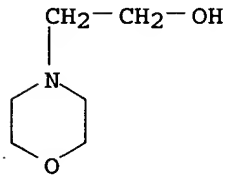
IT **622-40-2**, 4-(2-Hydroxyethyl)morpholine 24280-93-1, Mycophenolic acid
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate)

IT **128794-94-5P**
RL: **SPN (Synthetic preparation)**; **PREP (Preparation)**
(microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate)

IT 7631-86-9, Silica, uses
RL: **CAT (Catalyst use)**; USES (Uses)
(support; microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate)

IT **622-40-2**, 4-(2-Hydroxyethyl)morpholine
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate)

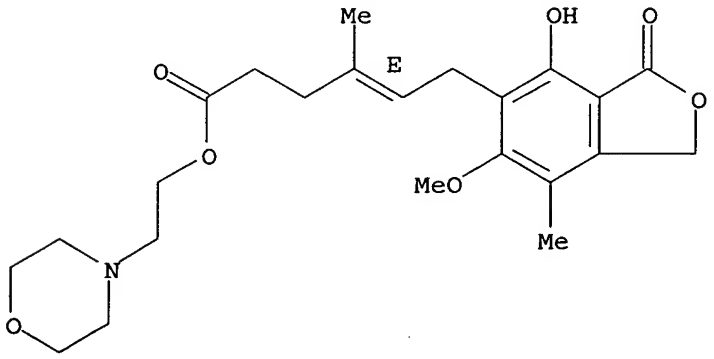
RN 622-40-2 CAPLUS
CN 4-Morpholineethanol (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



IT **128794-94-5P**
RL: **SPN (Synthetic preparation)**; **PREP (Preparation)**
(microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate)

RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

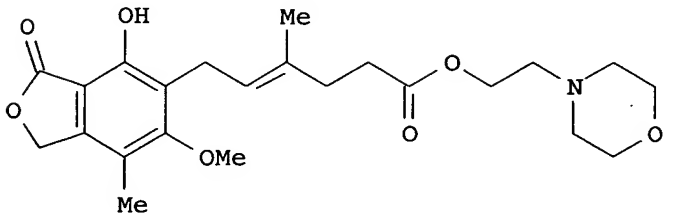


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

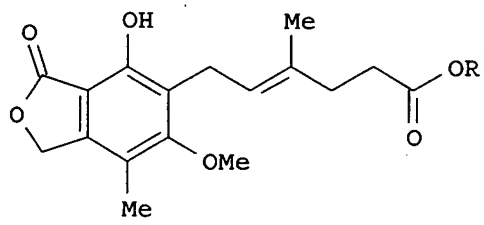
L19 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:701805 CAPLUS
DOCUMENT NUMBER: 141:225522
TITLE: Process for making mycophenolate mofetil by transesterification
INVENTOR(S): Lee, Kwang-chung; Lin, Shu-chuan; Chiu, Ray-hwa
PATENT ASSIGNEE(S): Taiwan
SOURCE: U.S. Pat. Appl. Publ., 3 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004167130	A1	20040826	US 2003-750466	20031229
TW 221414	B1	20041001	TW 2003-92103728	20030221
PRIORITY APPLN. INFO.:			TW 2003-92103728 A	20030221

OTHER SOURCE(S): CASREACT 141:225522; MARPAT 141:225522
GI



I



II

AB A process for making mycophenolate mofetil (I) comprising: conducting a **catalytic** transesterification by reacting a low-carbon alkyl ester of mycophenolic acid (II; R = Me, Et, Pr, Bu) with 2-morpholinoethanol [4-(2-hydroxyethyl)morpholine] to obtain a crude product of mycophenolate mofetil, which is then isolated and purified.

IC ICM A61K031-5377
ICS C07D413-02
INCL 514231500; 544147000
CC 28-13 (Heterocyclic Compounds (More Than One Hetero Atom))
ST transesterification process mycophenolate mofetil prepn; mycophenolic acid

ester transesterification morpholinoethanol process; tin oxide **catalyst** transesterification morpholinoethanol mycophenoliic acid ester

IT Transesterification **catalysts**
(process for preparation of mycophenolate mofetil by transesterification of mycophenolic acid esters with morpholinoethanol in presence of tin oxides)

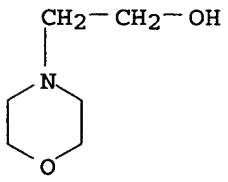
IT **818-08-6**, Dibutyltin oxide **21651-19-4**, Stannous oxide
RL: **CAT (Catalyst use)**; USES (Uses)
(process for preparation of mycophenolate mofetil by transesterification of mycophenolic acid esters with morpholinoethanol)

IT **622-40-2**, 4-(2-Hydroxyethyl)morpholine **31858-66-9**, Methyl mycophenolate **32483-51-5**, Ethyl mycophenolate **40336-78-5** **745067-13-4**
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(process for preparation of mycophenolate mofetil by transesterification of mycophenolic acid esters with morpholinoethanol)

IT **128794-94-5P**, Mycophenolate mofetil
RL: **SPN (Synthetic preparation)**; **PREP (Preparation)**
(process for preparation of mycophenolate mofetil by transesterification of mycophenolic acid esters with morpholinoethanol)

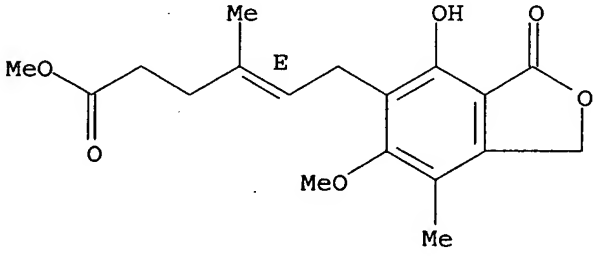
IT **622-40-2**, 4-(2-Hydroxyethyl)morpholine **31858-66-9**, Methyl mycophenolate **32483-51-5**, Ethyl mycophenolate **40336-78-5** **745067-13-4**
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(process for preparation of mycophenolate mofetil by transesterification of mycophenolic acid esters with morpholinoethanol)

RN 622-40-2 CAPLUS
CN 4-Morpholineethanol (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



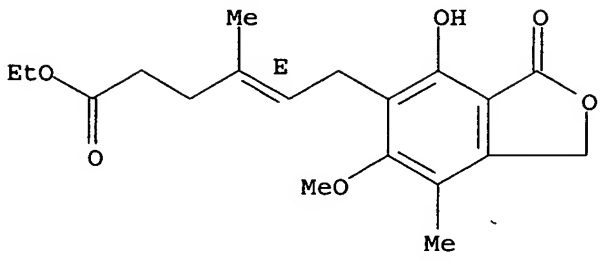
RN 31858-66-9 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, methyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



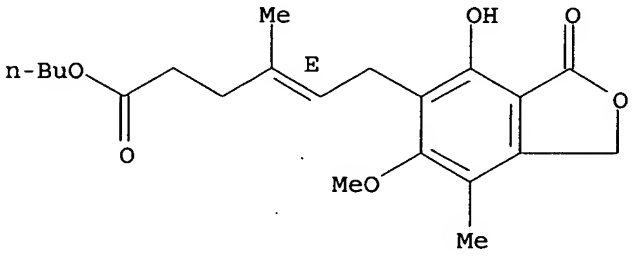
RN 32483-51-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



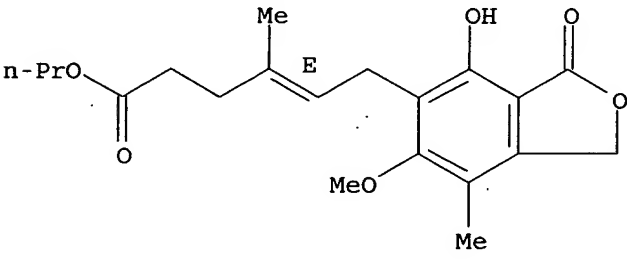
RN 40336-78-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, butyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



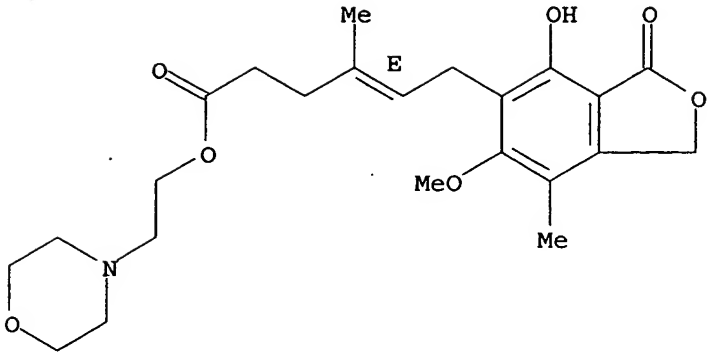
RN 745067-13-4 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, propyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **128794-94-5P**, Mycophenolate mofetil
RL: **SPN (Synthetic preparation)**; **PREP (Preparation)**
(process for preparation of mycophenolate mofetil by transesterification of mycophenolic acid esters with morpholinoethanol)
RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L19 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:397024 CAPLUS
DOCUMENT NUMBER: 138:384235
TITLE: Enzymatic preparation of mycophenolate mofetil
INVENTOR(S): Patil, Nitin; Mendhe, Rakesh; Khedkar, Anand; Melarkode, Ramakrishnan; Suryanarayan, Shrikumar
PATENT ASSIGNEE(S): Biocon India Limited, India
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003042393	A1	20030522	WO 2001-IN202	20011116

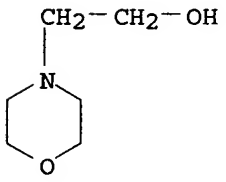
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2001-IN202 20011116
OTHER SOURCE(S): CASREACT 138:384235

AB The present invention relates to an improved method for synthesis of mycophenolate mofetil by reacting mycophenolic acid with an excess of 2-morpholinoethanol using an enzyme as **catalyst** in a water-free organic solvent and its subsequent purification The use of an anhydrous organic solvent leads to higher conversion of mycophenolic acid. Water generated in the reaction may also be removed using mol. sieves to further improve conversion of mycophenolic acid to mycophenolate mofetil.

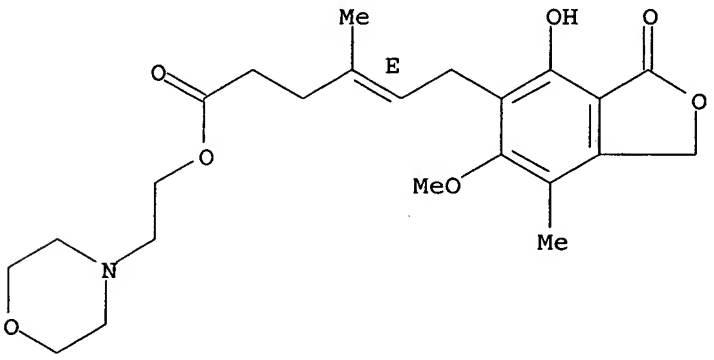
IC ICM C12P017-16
CC 16-2 (Fermentation and Bioindustrial Chemistry)
IT **622-40-2**, 2-Morpholinoethanol
RL: BCP (Biochemical process); **RCT (Reactant)**; BIOL (Biological study); PROC (Process); **RACT (Reactant or reagent)**
(enzymic preparation of mycophenolate mofetil)

IT **128794-94-5P**, Mycophenolate mofetil
RL: **BMF (Bioindustrial manufacture)**; **BPN (Biosynthetic preparation)**; **PUR (Purification or recovery)**; BIOL (Biological study); **PREP (Preparation)**
(enzymic preparation of mycophenolate mofetil)
IT 9001-62-1, Lipase
RL: **CAT (Catalyst use)**; USES (Uses)
(enzymic preparation of mycophenolate mofetil)
IT 471-34-1, Calcium carbonate, uses
RL: **CAT (Catalyst use)**; USES (Uses)
(lipase immobilization on calcium carbonate for enzymic preparation of mycophenolate mofetil)
IT **622-40-2**, 2-Morpholinoethanol
RL: BCP (Biochemical process); **RCT (Reactant)**; BIOL (Biological study); PROC (Process); **RACT (Reactant or reagent)**
(enzymic preparation of mycophenolate mofetil)
RN 622-40-2 CAPLUS
CN 4-Morpholineethanol (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



IT **128794-94-5P**, Mycophenolate mofetil
RL: **BMF (Bioindustrial manufacture)**; **BPN (Biosynthetic preparation)**; **PUR (Purification or recovery)**; BIOL (Biological study); **PREP (Preparation)**
(enzymic preparation of mycophenolate mofetil)
RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:964351 CAPLUS
DOCUMENT NUMBER: 138:24597
TITLE: Esterification process for the preparation of mycophenolic acid 2-(morpholino)ethyl ester using mycophenolic acid and 2-(morpholino)ethanol in a refluxing ether solvent
INVENTOR(S): Chudlik, Miloslav; Husek, Ales
PATENT ASSIGNEE(S): Ivax Corporation, USA; Galena AS
SOURCE: PCT Int. Appl., 8 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

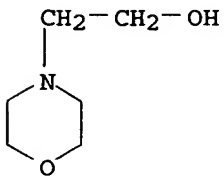
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002100855	A1	20021219	WO 2002-US18274	20020608
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CZ 292123	B6	20030813	CZ 2001-2071	20010608
CA 2450013	AA	20021219	CA 2002-2450013	20020608
EP 1421081	A1	20040526	EP 2002-756146	20020608
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2002010931	A	20040608	BR 2002-10931	20020608
JP 2004534063	T2	20041111	JP 2003-503622	20020608
US 2005085635	A1	20050421	US 2003-480058	20020608
PRIORITY APPLN. INFO.:			CZ 2001-2071 A	20010608
			WO 2002-US18274 W	20020608

OTHER SOURCE(S): CASREACT 138:24597; MARPAT 138:24597

AB An esterification process for the preparation of the immunosuppressant mycophenolic acid 2-(morpholino)ethyl ester (i.e., mycophenolate mofetil) using mycophenolic acid and 2-(morpholino)ethanol in a refluxing ether solvent (e.g., di-Bu ether) is described.

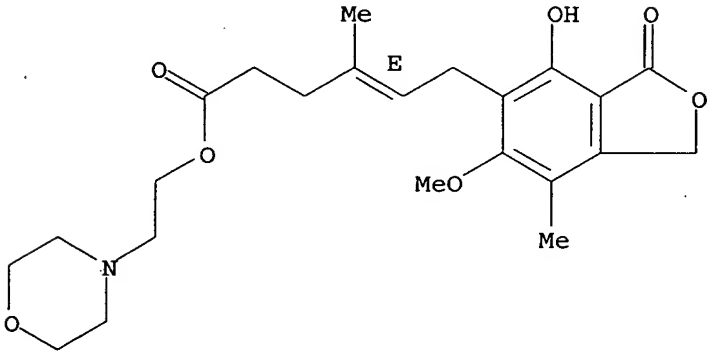
IC C07D413-02
CC 26-9 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 45
IT **622-40-2**, 2-(Morpholino)ethanol 24280-93-1, Mycophenolic acid
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(esterification process for the preparation of mycophenolic acid 2-(morpholino)ethyl ester using mycophenolic acid and 2-(morpholino)ethanol in a refluxing ether solvent)
IT **128794-94-5P**, Mycophenolate mofetil
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(esterification process for the preparation of mycophenolic acid 2-(morpholino)ethyl ester using mycophenolic acid and 2-(morpholino)ethanol in a refluxing ether solvent)
IT **622-40-2**, 2-(Morpholino)ethanol
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(esterification process for the preparation of mycophenolic acid

2-(morpholino)ethyl ester using mycophenolic acid and
2-(morpholino)ethanol in a refluxing ether solvent)
RN 622-40-2 CAPLUS
CN 4-Morpholineethanol (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



IT **128794-94-5P**, Mycophenolate mofetil
RL: **SPN (Synthetic preparation)**; **PREP (Preparation)**
(esterification process for the preparation of mycophenolic acid
2-(morpholino)ethyl ester using mycophenolic acid and
2-(morpholino)ethanol in a refluxing ether solvent)
RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:402025 CAPLUS
DOCUMENT NUMBER: 133:29685
TITLE: Methods of producing esters of mycophenolate
INVENTOR(S): Sircar, Anindya; Khedkar, Anand; Kulkarni, Madhav; Suryanarayan, Shrikumar; Sridharan, Madhavan; Acharaya, Poorpanapranja; Samvasivam, Ganesh
PATENT ASSIGNEE(S): Biocon India Limited, India
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000034503	A2	20000615	WO 1999-IN70	19991209
WO 2000034503	A3	20000817		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
IN 188985	A	20021130	IN 1998-MA2754	19981209
CA 2354554	AA	20000615	CA 1999-2354554	19991209
EP 1137795	A2	20011004	EP 1999-964770	19991209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6709846	B1	20040323	US 2001-857579	20010607
PRIORITY APPLN. INFO.:			IN 1998-MA2754 A	19981209
			WO 1999-IN70 W	19991209

OTHER SOURCE(S): CASREACT 133:29685

AB Methods for the manufacture of mycophenolate are disclosed. Mycophenolate mofetil is biochem. synthesized using mycophenolic acid and 2-morpholinoethanol with the help of an enzyme. Mycophenolate mofetil is also chemical synthesized non-**catalytically** by refluxing mycophenolic acid with 2-morpholinoethanol in the absence of a third solvent or a **catalyst**.

IC ICM C12P017-16

CC 16-2 (Fermentation and Bioindustrial Chemistry)
Section cross-reference(s): 26

IT **128794-94-5P**, Mycophenolate mofetil
RL: **BMF (Bioindustrial manufacture)**; **BPN (Biosynthetic preparation)**; **IMF (Industrial manufacture)**; **SPN (Synthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(producing esters of mycophenolate)

IT **622-40-2**, 2-Morpholinoethanol 24280-93-1, Mycophenolic acid
RL: BPR (Biological process); BSU (Biological study, unclassified); **RCT (Reactant)**; BIOL (Biological study); PROC (Process); **RACT (Reactant or reagent)**
(producing esters of mycophenolate)

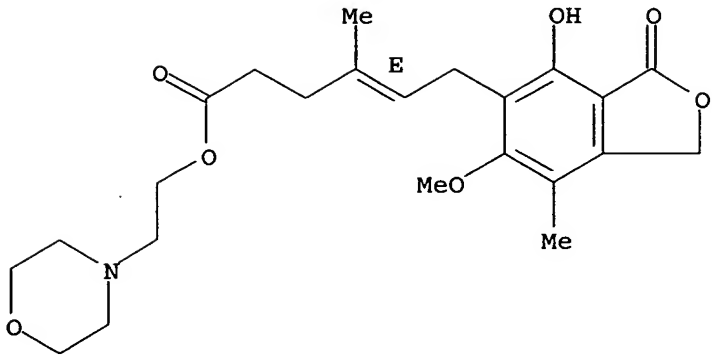
IT 9001-62-1, Lipase
RL: **CAT (Catalyst use)**; USES (Uses)
(producing esters of mycophenolate)

IT **128794-94-5P**, Mycophenolate mofetil
RL: **BMF (Bioindustrial manufacture)**; **BPN (Biosynthetic preparation)**; **IMF (Industrial manufacture)**; **SPN (Synthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(producing esters of mycophenolate)

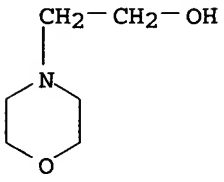
RN 128794-94-5 CAPLUS

CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **622-40-2**, 2-Morpholinoethanol
RL: BPR (Biological process); BSU (Biological study, unclassified); **RCT (Reactant)**; BIOL (Biological study); PROC (Process); **RACT (Reactant or reagent)**
(producing esters of mycophenolate)
RN 622-40-2 CAPLUS
CN 4-Morpholineethanol (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L19 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:32105 CAPLUS
DOCUMENT NUMBER: 124:105294
TITLE: Mycophenolate mofetil
AUTHOR(S): Sollinger, Hans W.
CORPORATE SOURCE: Department of Surgery, University of Wisconsin, Madison, WI, USA
SOURCE: Kidney International, Supplement (1995), 52, S14-S17
CODEN: KISUDF; ISSN: 0098-6577
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 23 refs. Mycophenolate mofetil (MMF), the morpholinoethyl ester of mycophenolic acid (MPA), is a new selective immunosuppressant used for the prevention and treatment of acute renal rejection after transplantation. In vivo MMF is deesterified to MPA, which is a potent and specific inhibitor of de novo purine synthesis and suppressor of both T and B lymphocyte proliferation. In animal studies, MMF has been shown to be effective in prolonging the survival of allografts and xenografts in rodents, dogs, and monkeys. Exptl. evidence in animal models suggests that MMF also may be effective in the treatment of chronic vascular rejection. A phase I clin. trial showed MMF was well tolerated in renal transplant patients at doses up to 3,500 mg/day for up to two years. There was no correlation between the incidence of adverse effects and dose of MMF, and no overt nephrotoxicity, hepatotoxicity, or myelotoxicity was observed In a multicenter study in patients with biopsy-proven renal

allograft rejection, successful rescue (stabilization or improvement of renal function) was achieved with MMF in combination with maintenance doses of cyclosporine and prednisone in 69% of patients. This result suggested that MMF may be effective in the treatment of renal allograft rejection after transplantation. In a large multicenter trial, MMF in combination with cyclosporine and prednisone was superior to a standard immunosuppressive regimen including azathioprine. Taken together, the data indicate that MMF will be a valuable addition to the list of immunosuppressants available for the prevention and treatment of renal rejection after transplantation.

CC 1-0 (Pharmacology)

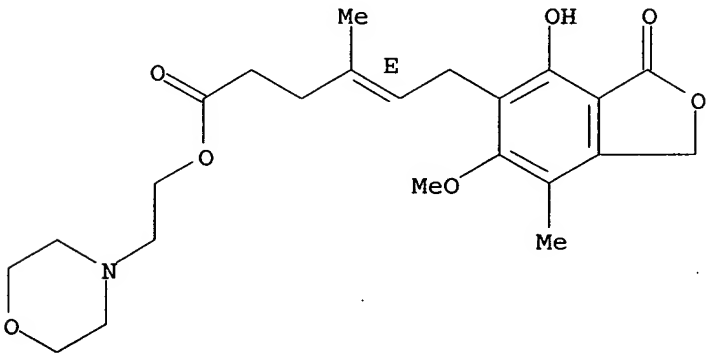
IT **128794-94-5P**, Mycophenolate mofetil
RL: ADV (Adverse effect, including toxicity); **SPN (Synthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(immunosuppressive effects of mycophenolate mofetil)

IT **128794-94-5P**, Mycophenolate mofetil
RL: ADV (Adverse effect, including toxicity); **SPN (Synthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(immunosuppressive effects of mycophenolate mofetil)

RN 128794-94-5 CAPLUS

CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L19 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:994342 CAPLUS

DOCUMENT NUMBER: 124:86709

TITLE: 5-substituted derivatives of mycophenolic acid

INVENTOR(S): Artis, Dean R.; Elworthy, Todd R.; Hawley, Ronald C.; Loughhead, David G.; Morgans, David J., Jr.; Nelson, Peter H.; Patterson, John W., Jr.; Rohloff, John C.; Sjogren, Eric B.; et al.

PATENT ASSIGNEE(S): Syntex (U.S.A.) Inc., USA

SOURCE: PCT Int. Appl., 142 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9522538	A1	19950824	WO 1995-US1787	19950216
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UG				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5493030	A	19960220	US 1994-198749	19940218
CA 2183530	AA	19950824	CA 1995-2183530	19950216
AU 9518754	A1	19950904	AU 1995-18754	19950216
ZA 9501299	A	19960816	ZA 1995-1299	19950216
EP 745073	A1	19961204	EP 1995-910984	19950216
EP 745073	B1	20000712		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1141038	A	19970122	CN 1995-191654	19950216
BR 9506819	A	19970909	BR 1995-6819	19950216
JP 09509174	T2	19970916	JP 1995-521868	19950216
IL 112665	A1	19990509	IL 1995-112665	19950216
IL 124139	A1	20000229	IL 1995-124139	19950216
TW 384288	B	20000311	TW 1995-84101398	19950216
AT 194608	E	20000715	AT 1995-910984	19950216
ES 2149971	T3	20001116	ES 1995-910984	19950216
PT 745073	T	20001229	PT 1995-910984	19950216
HR 950070	B1	20010228	HR 1995-950070	19950216
US 5633279	A	19970527	US 1995-483042	19950606
FI 9603218	A	19961011	FI 1996-3218	19960816
GR 3033864	T3	20001031	GR 2000-401101	20000713
PRIORITY APPLN. INFO.:			US 1994-198749 A	19940218
			IL 1995-112665 A3	19950216
			WO 1995-US1787 W	19950216

OTHER SOURCE(S): MARPAT 124:86709
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A pharmaceutical composition comprising 5-substituted derivs. I of mycophenolic acid, where R1 = H, COR10, R10 = lower alkyl, aryl or NH-aryl; Z = CH2CH:CZ1CHZ2CZ3Z4COG, ZB, ZC, ZD, ZE, ZF, ZG, or ZH; Z1 = H, lower alkyl, halo, CF3; Z2 = H, OH, lower alkyl, lower alkoxy, aryl, or CH2Z13, Z13 = halo, CN, aryl, heteroaryl; Z3 = H, OH, lower alkyl, lower alkenyl, lower alkoxy, halo, Ph, P(O)(OMe)2, P(O)(OH)(OMe), NHZ11, SH, SOmZ12, Z11 = H, alkyl, acyl lower alkyl sulfonyl, Z12 = lower alkyl, m = 0-2; Z4 = H, OH, lower alkyl, halo, Ph, where Z4 is not OH or halo when Z3 = OH, halo, P(O)(OMe)2, P(O)(OH)(OMe), NHZ11, SZ12; Z3Z4 = cycloalkyl of 3-5 carbons; G = OH, lower alkoxy, lower thioalkyl, NG1G2, O(CH2)nNG1G2, O(CH2)nN:G3, n = 1-6, G1,G2 = H, lower alkyl, :G3 = lower alkylene of 4-6 carbons or of 3-5 carbons and one of O, S, NG4, G4 = H, lower alkyl; provided that when Z1 = Me, Z2, Z3 and Z4 are not all H and when R1, Z3, Z4 are all H and Z1 = Me, Z2 is not H or OH; for ZB, Z5 = H or lower alkyl; Z8 = H, lower alkyl or forms double bond with D2; D1D2 form a substituted or unsatd. or unsatd. carbocyclic or heterocyclic ring of 3-7 atoms; for ZC, Z8 = H or lower alkyl; for ZD, D3 = CH2 CH2CH2; for ZE, Z6 = H, lower alkyl, lower alkoxy, CO2H, NH2, N3, or halo; Z7 = H, lower alkyl, lower alkoxy, or halo; for ZH, D4 = (CH2)y, O, OCH2, y = 1-3. The disclosed hexenoic acid

side-chain derivs. of mycophenolic acid are therapeutic agents advantageous in the treatment of disease states indicated for mycophenolic acid and/or mycophenolate mofetil, including immune, inflammatory, tumor, proliferative, viral or psoriatic disorders.

IC ICM C07D307-88
ICS C07D413-06; C07D407-06; C07D409-06; C07D405-06; A61K031-365; A61K031-42

CC 26-9 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1

IT **128794-94-5DP**, Mycophenolate mofetil, 5-substituted analogs
171962-44-0P 172151-03-0P 172151-05-2P 172151-10-9P 172151-11-0P
172151-12-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **IMF (Industrial manufacture)**; **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of 5-substituted derivs. of mycophenolic acid as therapeutic agents for treatment of disease states)

IT 78-39-7, Triethyl orthoacetate 97-62-1, Ethyl isobutyrate 105-53-3, Diethyl malonate 115-80-0, Triethyl orthopropionate 311-46-6, Ethyl (dimethyl phosphono)acetate 1730-25-2 3886-69-9 24280-93-1, Mycophenolic acid 24720-64-7 24823-81-2, Trimethyl orthopropionate **31858-66-9** 33375-06-3 37609-33-9, (Cyclopenten-1-yl)magnesium bromide 40682-54-0, Ethyl N-benzylideneglycinate 55444-67-2, Trimethyl 4-bromoorthobutyrate 89028-40-0 90719-32-7, (S)-4-Benzyl-2-oxazolidinone 97872-61-2 112022-83-0 131001-86-0 150456-43-2
172151-37-0 **172151-41-6 172151-44-9**
172151-52-9 172151-57-4 172151-60-9 172151-74-5
172151-85-8 172151-88-1 172151-97-2 172152-09-9 172152-11-3
172152-20-4
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(preparation of 5-substituted derivs. of mycophenolic acid as therapeutic agents for treatment of disease states)

IT 24953-95-5P 111512-13-1P **125198-47-2P** 138768-41-9P
138768-42-0P **172151-13-2P 172151-15-4P**
172151-16-5P 172151-39-2P **172151-45-0P** 172151-47-2P
172151-48-3P 172151-49-4P 172151-50-7P **172151-55-2P**
172151-61-0P 172151-62-1P 172151-63-2P 172151-65-4P 172151-66-5P
172151-68-7P 172151-70-1P 172151-72-3P 172151-73-4P
172151-75-6P 172151-77-8P 172151-78-9P 172151-86-9P 172151-87-0P
172151-89-2P 172151-90-5P 172151-91-6P 172151-92-7P 172151-93-8P
172151-94-9P 172151-95-0P 172151-99-4P 172152-13-5P
172152-14-6P 172152-15-7P 172152-16-8P
172152-17-9P 172152-18-0P 172276-17-4P 172276-18-5P
172487-10-4P
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(preparation of 5-substituted derivs. of mycophenolic acid as therapeutic agents for treatment of disease states)

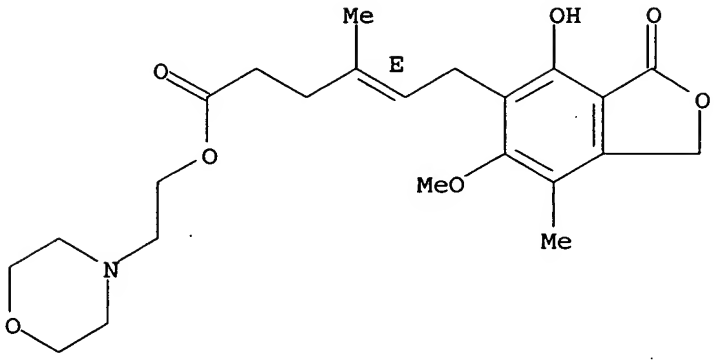
IT **128794-94-5DP**, Mycophenolate mofetil, 5-substituted analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **IMF (Industrial manufacture)**; **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of 5-substituted derivs. of mycophenolic acid as therapeutic agents for treatment of disease states)

RN 128794-94-5 CAPLUS

CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA

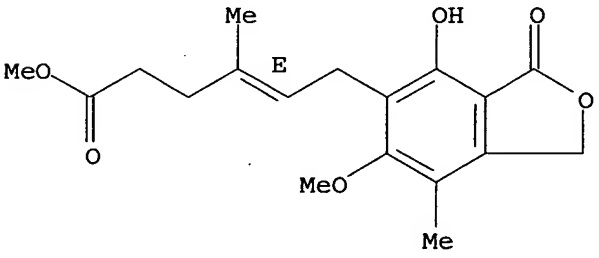
INDEX NAME)

Double bond geometry as shown.



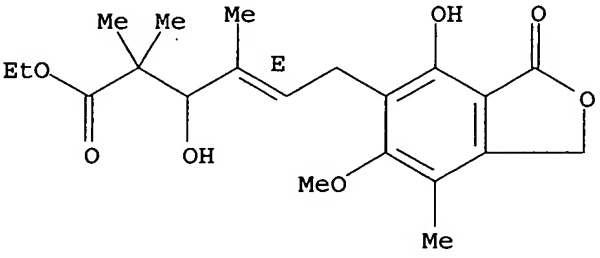
IT **31858-66-9 172151-41-6 172151-44-9**
172151-52-9 172151-57-4
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(preparation of 5-substituted derivs. of mycophenolic acid as therapeutic agents for treatment of disease states)
RN 31858-66-9 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, methyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



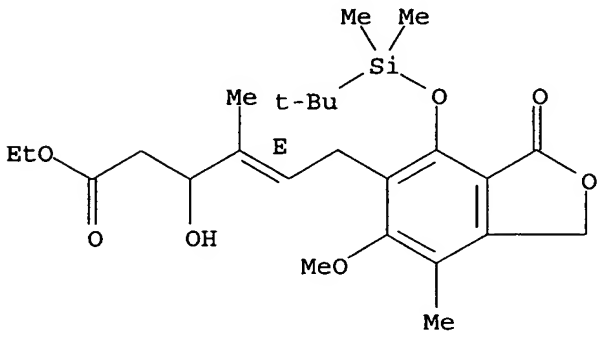
RN 172151-41-6 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-3-hydroxy-2,2,4-trimethyl-, ethyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



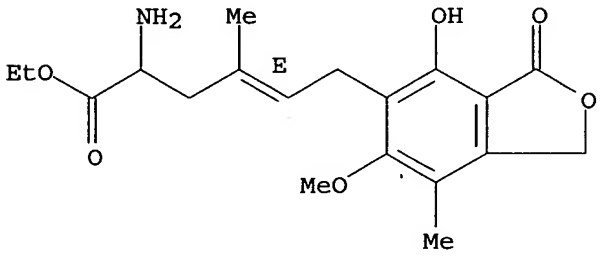
RN 172151-44-9 CAPLUS
CN 4-Hexenoic acid, 6-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,3-dihydro-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-3-hydroxy-4-methyl-, ethyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



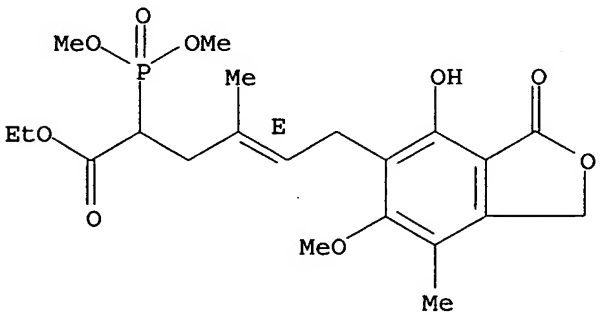
RN 172151-52-9 CAPLUS
CN 4-Hexenoic acid, 2-amino-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, ethyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 172151-57-4 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-2-(dimethoxyphosphinyl)-4-methyl-, ethyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

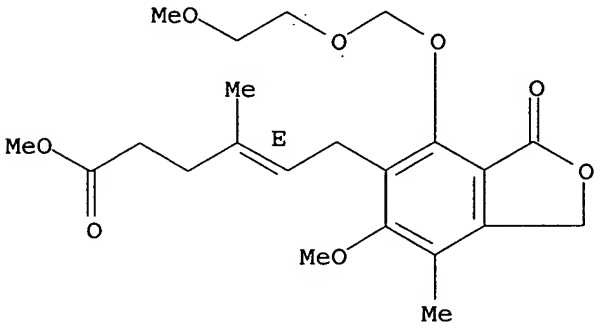


IT **125198-47-2P 172151-13-2P 172151-15-4P**

172151-16-5P 172151-45-0P 172151-55-2P
172151-68-7P 172152-14-6P 172152-15-7P
172152-16-8P 172152-17-9P
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(preparation of 5-substituted derivs. of mycophenolic acid as therapeutic agents for treatment of disease states)

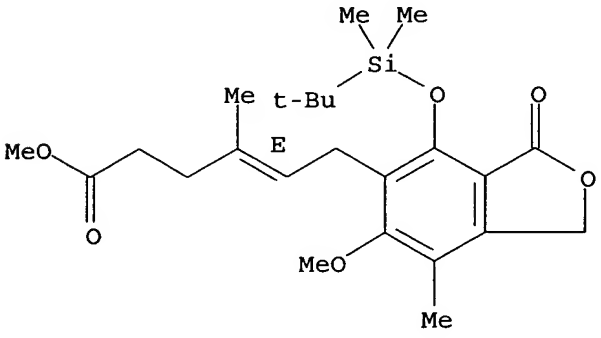
RN 125198-47-2 CAPLUS
CN 4-Hexenoic acid, 6-[1,3-dihydro-6-methoxy-4-[(2-methoxyethoxy)methoxy]-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-, methyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



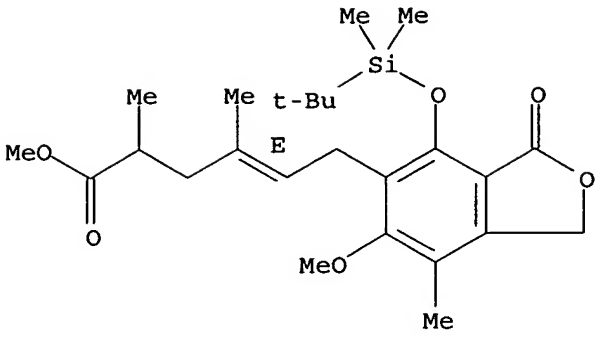
RN 172151-13-2 CAPLUS
CN 4-Hexenoic acid, 6-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,3-dihydro-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-, methyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



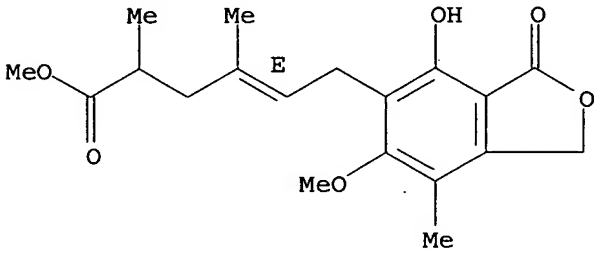
RN 172151-15-4 CAPLUS
CN 4-Hexenoic acid, 6-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,3-dihydro-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-2,4-dimethyl-, methyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



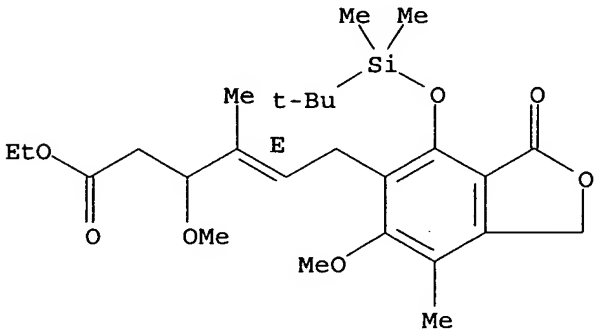
RN 172151-16-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-2,4-dimethyl-, methyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



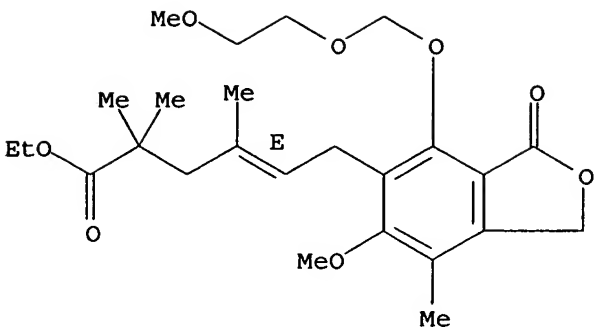
RN 172151-45-0 CAPLUS
CN 4-Hexenoic acid, 6-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,3-dihydro-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-3-methoxy-4-methyl-, ethyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

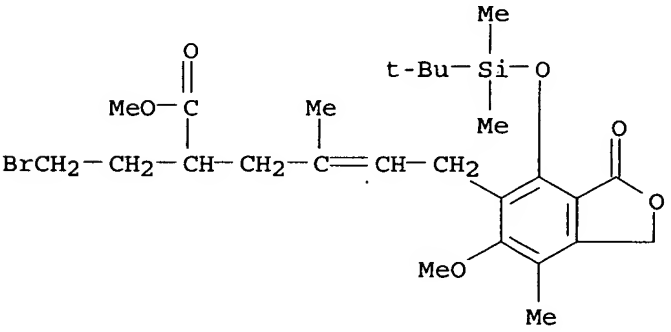


RN 172151-55-2 CAPLUS
CN 4-Hexenoic acid, 6-[1,3-dihydro-6-methoxy-4-[(2-methoxyethoxy)methoxy]-7-methyl-3-oxo-5-isobenzofuranyl]-2,2,4-trimethyl-, ethyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

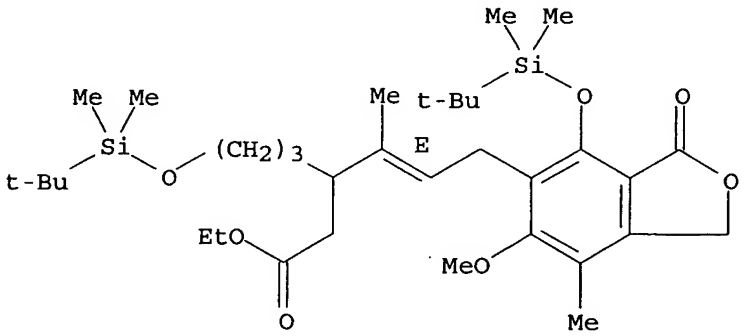


RN 172151-68-7 CAPLUS
CN 4-Hexenoic acid, 2-(2-bromoethyl)-6-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,3-dihydro-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-, methyl ester (9CI) (CA INDEX NAME)



RN 172152-14-6 CAPLUS
CN 4-Hexenoic acid, 6-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,3-dihydro-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-3-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-4-methyl-, ethyl ester, (E)- (9CI) (CA INDEX NAME)

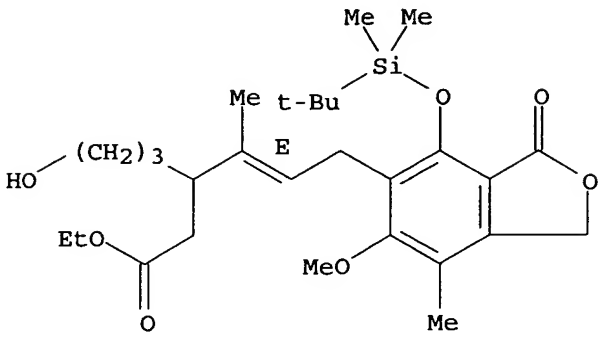
Double bond geometry as shown.



RN 172152-15-7 CAPLUS
CN 4-Hexenoic acid, 6-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,3-dihydro-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-3-(3-hydroxypropyl)-4-methyl-,

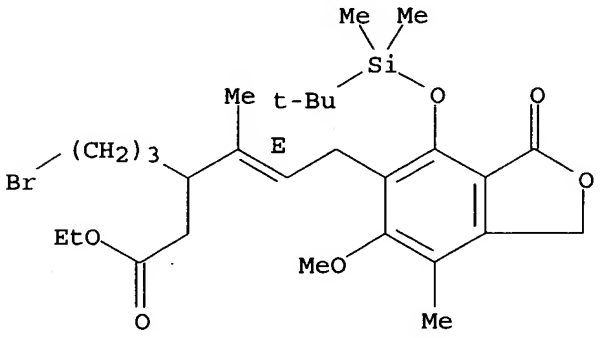
ethyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



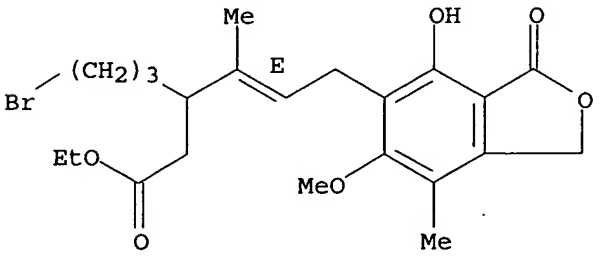
RN 172152-16-8 CAPLUS
CN 4-Hexenoic acid, 3-(3-bromopropyl)-6-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,3-dihydro-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-, ethyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 172152-17-9 CAPLUS
CN 4-Hexenoic acid, 3-(3-bromopropyl)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, ethyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L19 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:576681 CAPLUS
DOCUMENT NUMBER: 122:322496
TITLE: Crystalline anhydrous mycophenolate mofetil and intravenous formulation thereof
INVENTOR(S): Fu, Roger Cherng; Leung, De-Mei; Fleitman, Jeffrey S.; Rizzolio, Michele C.
PATENT ASSIGNEE(S): Syntex (U.S.A) Inc., USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9507902	A1	19950323	WO 1994-US10142	19940912
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2171836	AA	19950323	CA 1994-2171836	19940912
AU 9477238	A1	19950403	AU 1994-77238	19940912
AU 677435	B2	19970424		
EP 724581	A1	19960807	EP 1994-928054	19940912
EP 724581	B1	19981118		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1131420	A	19960918	CN 1994-193413	19940912
CN 1060770	B	20010117		
BR 9407469	A	19961112	BR 1994-7469	19940912
HU 75119	A2	19970428	HU 1996-652	19940912
HU 217300	B	19991228		
AT 173475	E	19981215	AT 1994-928054	19940912
ES 2123831	T3	19990116	ES 1994-928054	19940912
RU 2132849	C1	19990710	RU 1996-107396	19940912
PL 178522	B1	20000531	PL 1994-313480	19940912
RO 118075	B1	20030130	RO 1996-567	19940912
RO 118427	B1	20030530	RO 2002-200201154	19940912
CZ 292423	B6	20030917	CZ 1996-788	19940912
ZA 9407088	A	19960314	ZA 1994-7088	19940914
IL 110970	A1	19990126	IL 1994-110970	19940914
FI 9601169	A	19960313	FI 1996-1169	19960313
NO 9601075	A	19960315	NO 1996-1075	19960315
NO 314727	B1	20030512		
LV 11326	B	19961020	LV 1996-85	19960315
LT 4052	B	19961025	LT 1996-28	19960315
HK 1012624	A1	20000407	HK 1998-113833	19981217

PRIORITY APPLN. INFO.: US 1993-121841 A 19930915
WO 1994-US10142 W 19940912

AB The crystalline anhydrous compound of mycophenolate mofetil (I) wherein the compound is complexed as a salt with an anion selected from the group consisting of chloride, sulfate, phosphate and acetate, in particular the hydrochloride salt, and compns., i.v. formulations, and a kit thereof are disclosed. I 38.0 was dissolved in isopropanol 200 mL and the solution was added to a solution of HCl 10.0 g in isopropanol 150 mL to obtain hydrochloride salt which was collected by filtration and dried under vacuum. The crystalline anhydrous form of I.HCl was prepared by heating the crystalline monohydrate

hydrochloride from I.HCl at 60° for 30 min. The solubility of anhydrous I.HCl was 84mg/mL as compared to 40 mg/mL for crystalline monohydrate form.

IC ICM C07D307-88
ICS A61K031-535

CC 63-5 (Pharmaceuticals)

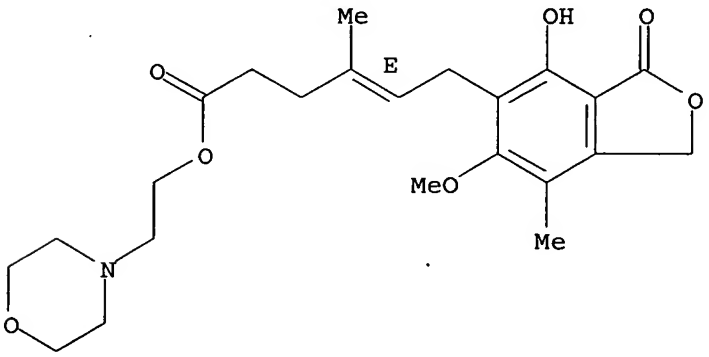
IT **116680-01-4P**, Mycophenolate mofetil hydrochloride 163392-62-9P 163392-63-0P 163392-64-1P
RL: **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(i.v. pharmaceuticals containing crystalline anhydrous mycophenolate mofetil)

IT **116680-01-4P**, Mycophenolate mofetil hydrochloride
RL: **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(i.v. pharmaceuticals containing crystalline anhydrous mycophenolate mofetil)

RN 116680-01-4 CAPLUS

CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, hydrochloride, (4E)- (9CI) (CA INDEX NAME)

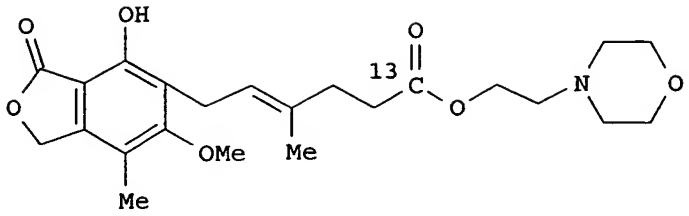
Double bond geometry as shown.



Vol. 36 QD466.56

L19 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:548349 CAPLUS
DOCUMENT NUMBER: 123:111784
TITLE: Synthesis of mycophenolate mofetil-[14C], RS-61443-14C
AUTHOR(S): Huang, Glenn T.; Parnes, Howard
CORPORATE SOURCE: Institute Organic Chemistry, Syntex Discovery Research, Palo Alto, CA, 94303, USA
SOURCE: Journal of Labelled Compounds & Radiopharmaceuticals (1995), 36(5), 449-56
CODEN: JLCRD4; ISSN: 0362-4803
PUBLISHER: Wiley
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Synthesis of the potent immunosuppressive agent, mycophenolate mofetil (I) labeled with carbon-14 is described. Methoxyethoxymethyl (MEM) protected mycophenolate norbromide was prepared from unlabeled mycophenolic acid using a modified Hunsdiecker reaction. A three step synthesis furnished the title compound, having a specific activity of 53.8 mCi/mmol, in 49.5% overall yield from K14CN.

CC 27-7 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 28

IT **622-40-2**, 4-(2-Hydroxyethyl)morpholine 1121-30-8, 1-Hydroxy-2-pyridinethione 24280-93-1
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(synthesis of mycophenolate mofetil-[14C])

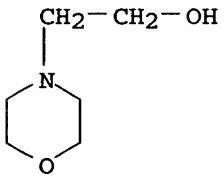
IT **31858-66-9P 125198-47-2P** 165684-38-8P 165684-41-3P 165684-42-4P 165684-43-5P 165684-45-7P 165684-46-8P
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(synthesis of mycophenolate mofetil-[14C])

IT 165684-39-9P 165684-40-2P 165684-44-6P **165684-47-9P**
RL: **SPN (Synthetic preparation)**; **PREP (Preparation)**
(synthesis of mycophenolate mofetil-[14C])

IT **622-40-2**, 4-(2-Hydroxyethyl)morpholine
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(synthesis of mycophenolate mofetil-[14C])

RN 622-40-2 CAPLUS

CN 4-Morpholineethanol (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

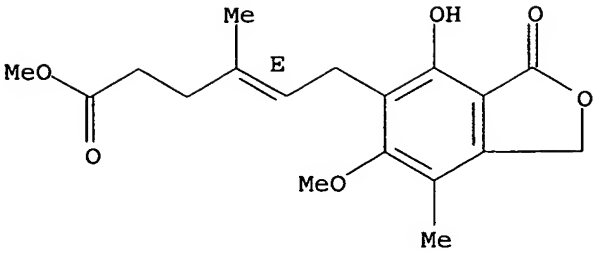


IT **31858-66-9P 125198-47-2P**
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(synthesis of mycophenolate mofetil-[14C])

RN 31858-66-9 CAPLUS

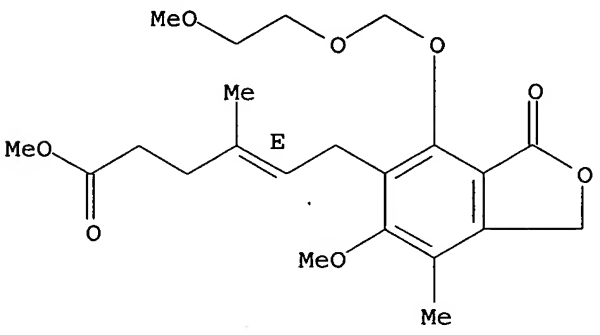
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, methyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



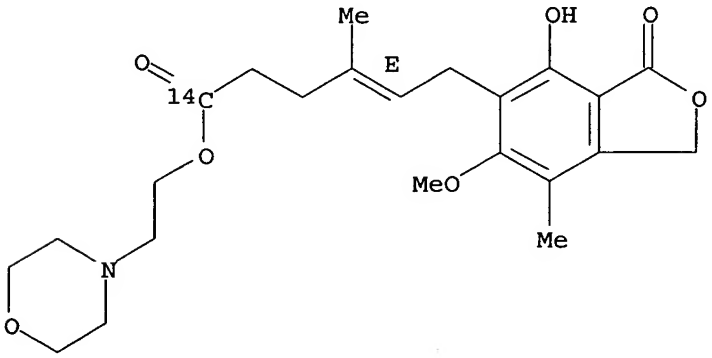
RN 125198-47-2 CAPLUS
CN 4-Hexenoic acid, 6-[1,3-dihydro-6-methoxy-4-[(2-methoxyethoxy)methoxy]-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-, methyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **165684-47-9P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(synthesis of mycophenolate mofetil-[14C])
RN 165684-47-9 CAPLUS
CN 4-Hexenoic-1-14C acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



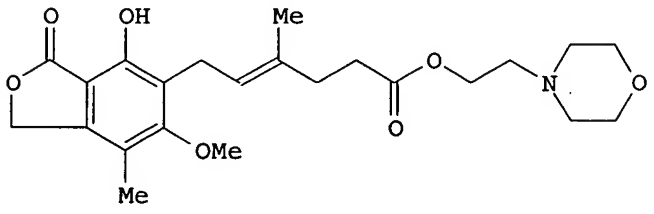
L19 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:8601 CAPLUS
DOCUMENT NUMBER: 120:8601
TITLE: Direct esterification of mycophenolic acid
INVENTOR(S): Knox, Martin; Donegan, Gregory; Smith, Dennis A.
PATENT ASSIGNEE(S): Syntex (U.S.A.), Inc., USA
SOURCE: U.S., 6 pp. Cont.-in-part of U.S. Ser. No. 911,635, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5247083	A	19930921	US 1992-993146	19921218
WO 9401427	A1	19940120	WO 1993-US6390	19930709
W: JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 649422	A1	19950426	EP 1993-917003	19930709
EP 649422	B1	19970319		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08500340	T2	19961116	JP 1994-503484	19930709
JP 3199741	B2	20010820		
AT 150460	E	19970415	AT 1993-917003	19930709
ES 2098763	T3	19970501	ES 1993-917003	19930709

PRIORITY APPLN. INFO.:
US 1992-911635 B2 19920710
US 1992-993146 A 19921218
WO 1993-US6390 W 19930709

OTHER SOURCE(S): CASREACT 120:8601
GI

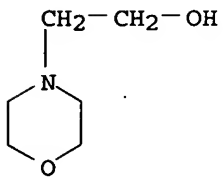


I

AB A process for the esterification of mycophenolic acid with 2-morpholinoethanol in an inert organic solvent (e.g., toluene/xylene) capable of azeotropic removal of water gave product, the immunosuppressive drug mycophenolate mofetil (I). Yields were 78-83%. Inclusion of an acid or base **catalyst** in the reaction gave no increase in either completion or yield, and is thus unnecessary. Addnl. solvents are benzene, mineral spirits, and CH2Cl2.

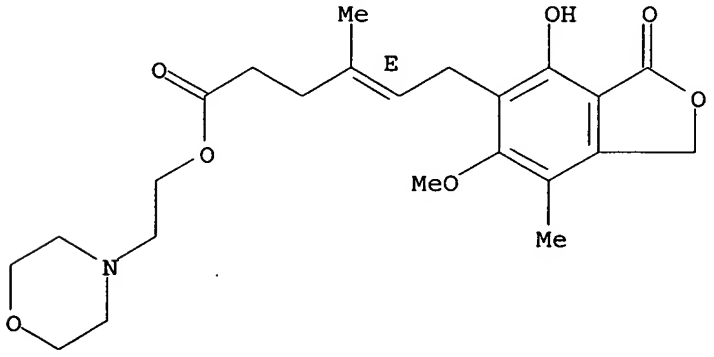
IC ICM C07D413-12
INCL 544153000
CC 28-13 (Heterocyclic Compounds (More Than One Hetero Atom))
IT 104-15-4, Toluene sulfonic acid, uses 121-44-8, Triethylamine, uses 280-57-9, Triethylenediamine 7664-93-9, Sulfuric acid, uses
RL: **CAT (Catalyst use)**; USES (Uses)
(**catalyst**, in esterification of mycophenolic acid with

morpholinoethanol to give mycophenolate mofetil)
IT **622-40-2**, 2-Morpholinoethanol
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(esterification by, of mycophenolic acid)
IT **128794-94-5P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation of, by direct esterification)
IT **622-40-2**, 2-Morpholinoethanol
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(esterification by, of mycophenolic acid)
RN 622-40-2 CAPLUS
CN 4-Morpholineethanol (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



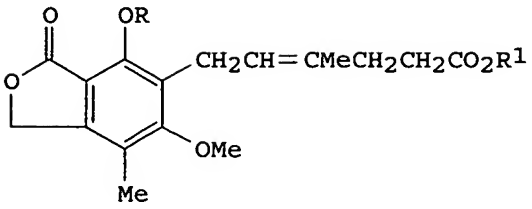
IT **128794-94-5P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation of, by direct esterification)
RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

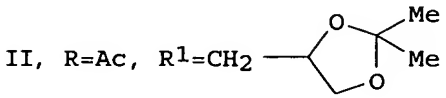


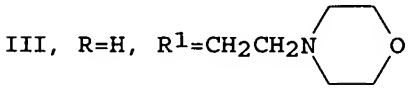
L19 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:164868 CAPLUS
DOCUMENT NUMBER: 112:164868
TITLE: Bioavailability improvement of mycophenolic acid through amino ester derivatization
AUTHOR(S): Lee, William A.; Gu, Leo; Miksztal, Andrew R.; Chu, Nancy; Leung, Kwan; Nelson, Peter H.
CORPORATE SOURCE: Inst. Pharm. Sci., Syntex Res., Palo Alto, CA, USA
SOURCE: Pharmaceutical Research (1990), 7(2), 161-6
CODEN: PHREEB; ISSN: 0724-8741
DOCUMENT TYPE: Journal

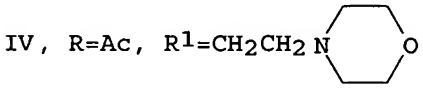
LANGUAGE: English
GI



I, R=R1=H







AB The potential bioavailability improvement of mycophenolic acid (I), through ester derivatization was evaluated in monkeys at a dose of 20 mg/kg in this study. The acetyl solketal ester (II) had excellent partition properties but poor aqueous solubility Thus, even though it can be converted rapidly to I by plasma and liver enzymes, it showed poor oral bioavailability (56% of I) in monkeys. The bioavailability of the morpholinoethyl ester III and the acetyl morpholinoethyl ester IV, on the other hand, were 236 and 150% that of I, resp. Since ester IV has greater aqueous solubility, but similar chemical stability and enzymic hydrolysis rates compared to ester III, the better bioavailability of ester I may result from its greater partitioning into the gastrointestinal membranes.

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 27

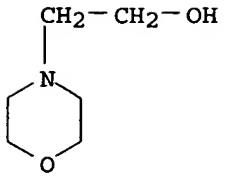
IT 100-79-8, Solketal **622-40-2**, 4-Morpholineethanol
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(esterification by, of mycophenolic acid chloride)

IT **116680-01-4P** 116680-05-8P 126269-40-7P
RL: **SPN (Synthetic preparation)**; **PREP (Preparation)**
(preparation and bioavailability of, as mycophenolic acid prodrug)

IT **622-40-2**, 4-Morpholineethanol
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(esterification by, of mycophenolic acid chloride)

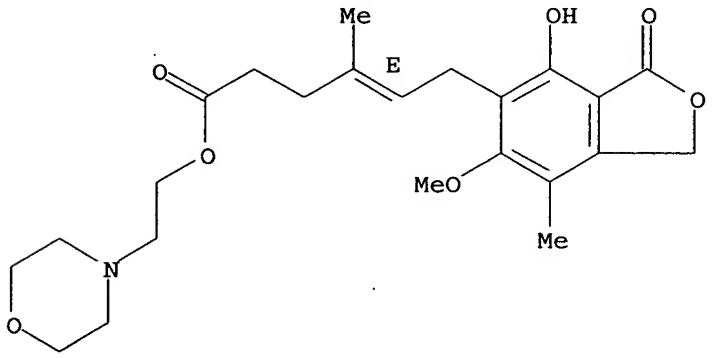
RN 622-40-2 CAPLUS

CN 4-Morpholineethanol (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



IT **116680-01-4P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation and bioavailability of, as mycophenolic acid prodrug)
RN 116680-01-4 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, hydrochloride, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



● HCl

L19 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:549226 CAPLUS
DOCUMENT NUMBER: 109:149226
TITLE: Preparation of morpholinoethyl esters of mycophenolic acid and pharmaceutical compositions containing them as immunosuppressive and antiinflammatory agents
INVENTOR(S): Nelson, Peter H.; Gu, Chee Liang L.; Allison, Anthony C.; Eugui, Elsie M.; Lee, William A.
PATENT ASSIGNEE(S): Syntex (U.S.A.), Inc., USA
SOURCE: U.S., 9 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4753935	A	19880628	US 1987-8717	19870130
US 4808592	A	19890228	US 1987-93459	19870904
DK 8706587	A	19880731	DK 1987-6587	19871215

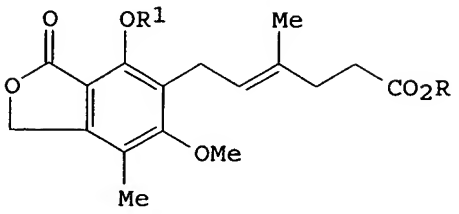
DK 166675	B1	19930628		
FI 8705502	A	19880731	FI 1987-5502	19871215
FI 85141	B	19911129		
FI 85141	C	19920310		
NO 8705240	A	19880801	NO 1987-5240	19871215
NO 171680	B	19930111		
NO 171680	C	19930421		
AU 8782540	A1	19880804	AU 1987-82540	19871215
AU 599728	B2	19900726		
JP 63188672	A2	19880804	JP 1987-320066	19871215
JP 05071591	B4	19931007		
EP 281713	A1	19880914	EP 1987-311021	19871215
EP 281713	B1	19911009		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
HU 47567	A2	19890328	HU 1987-5663	19871215
HU 201927	B	19910128		
ZA 8709414	A	19890830	ZA 1987-9414	19871215
AT 68180	E	19911015	AT 1987-311021	19871215
IL 84833	A1	19920329	IL 1987-84833	19871215
ES 2038190	T3	19930716	ES 1987-311021	19871215
CA 1333285	A1	19941129	CA 1987-554352	19871215
US 4786637	A	19881122	US 1988-146883	19880122
US 4868153	A	19890919	US 1988-233200	19880817
US 4952579	A	19900828	US 1988-272161	19881114
US 4948793	A	19900814	US 1989-373413	19890629
US 4992467	A	19910212	US 1990-500439	19900328
HU 210350	B	19950328	HU 1994-8	19940701

PRIORITY APPLN. INFO.:

US 1987-8717	A3	19870130
US 1987-93459	A3	19870904
EP 1987-311021	A	19871215
US 1988-146883	A3	19880122
US 1988-233200	A3	19880817
US 1988-272161	A3	19881114
US 1989-373413	A3	19890629

OTHER SOURCE(S): MARPAT 109:149226

GI

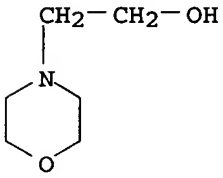


I

AB The title esters [I; R = 2-morpholinoethyl (Q); R1 = H, alkanoyl, aroyl] were prepared as immunosuppressants and antiinflammatories (no data) by esterification of mycophenolic acid (I, R = R1 = H) with QOH, followed by optional esterification of the free OH. I (R = R1 = H) was treated with SOCl2 in CH2Cl2 to give the acid chloride which was added to QOH in CH2Cl2 at 4° to give I (R = Q, R1 = H), converted to its hydrochloride (II). Capsules were prepared, each containing II 200, lactose 148, and Mg stearate 2 mg.

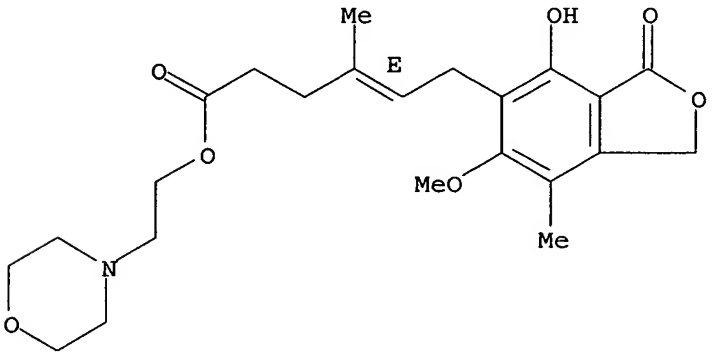
IC ICM A61K031-535
ICS C07D413-12

INCL 514233500
CC 26-6 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 28, 63
IT **622-40-2**, 4-Morpholineethanol
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(esterification by, of mycophenolic acid chloride)
IT **116680-01-4P 116680-02-5P 116680-03-6P**
116680-04-7P 116680-05-8P 116680-06-9P 116680-07-0P 116680-08-1P
128794-94-5P
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation of, as antiinflammatory and immunosuppressant)
IT **622-40-2**, 4-Morpholineethanol
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(esterification by, of mycophenolic acid chloride)
RN 622-40-2 CAPLUS
CN 4-Morpholineethanol (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



IT **116680-01-4P 116680-02-5P 116680-03-6P**
128794-94-5P
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation of, as antiinflammatory and immunosuppressant)
RN 116680-01-4 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, hydrochloride, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



● HCl

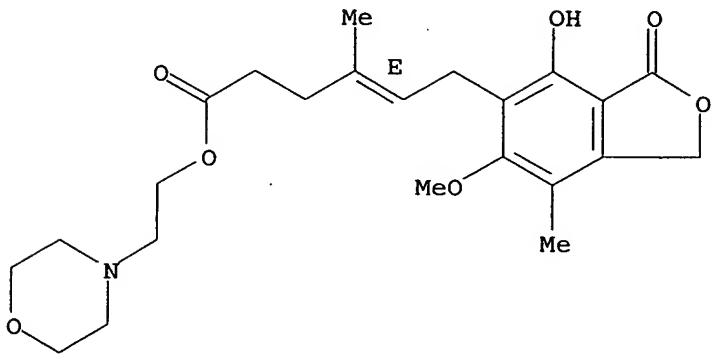
RN 116680-02-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (E)-, sulfate

(2:1) (salt) (9CI) (CA INDEX NAME)

CM 1

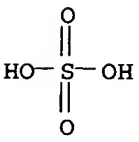
CRN 128794-94-5
CMF C23 H31 N O7

Double bond geometry as shown.



CM 2

CRN 7664-93-9
CMF H2 O4 S

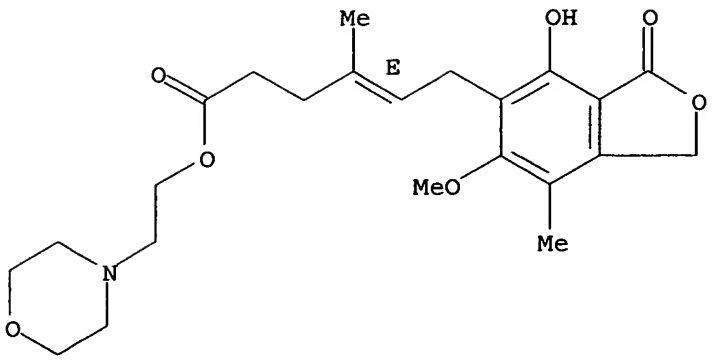


RN 116680-03-6 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (E)-, sulfate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

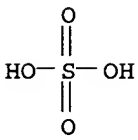
CRN 128794-94-5
CMF C23 H31 N O7

Double bond geometry as shown.



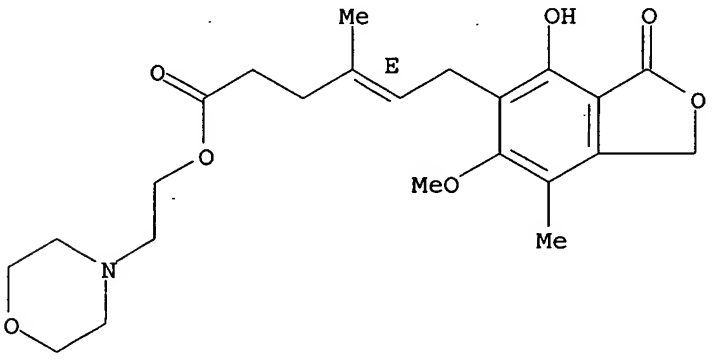
CM 2

CRN 7664-93-9
CMF H2 O4 S



RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L19 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:422760 CAPLUS
DOCUMENT NUMBER: 109:22760
TITLE: Preparation of heterocyclic aminoalkyl esters of mycophenolic acid as immunosuppressive agents, antiinflammatories, and virucides
INVENTOR(S): Nelson, Peter H.; Gu, Chee Liang L.; Allison, Anthony

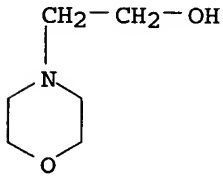
C.; Eugui, Elsie M.; Lee, William A.
PATENT ASSIGNEE(S): Syntex (U.S.A.), Inc., USA
SOURCE: U.S., 16 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4727069	A	19880223	US 1987-8909	19870130
US 4748173	A	19880531	US 1987-99950	19870923
US 4861776	A	19890829	US 1988-160212	19880225
US 5177072	A	19930105	US 1991-809084	19911209

PRIORITY APPLN. INFO.:

US 1987-8909	A3	19870130
US 1987-99950	A3	19870923
US 1988-160212	A3	19880225
US 1989-358775	B1	19890530

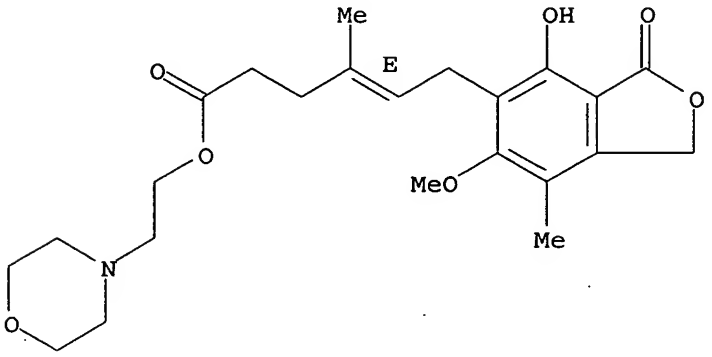
OTHER SOURCE(S): MARPAT 109:22760
GI For diagram(s), see printed CA Issue.
AB The title compds. (I; R = R1CO; R1 = C≥7 cycloalkyl, R2R3N; R2 = H, alkyl; R3 = R2O2CC6H4, R2; Y = C4-6 alkylene, C3-5 alkylene plus 1 O, S, or R5N; R5 = H, C1-5 alkyl; m = 2-4) and their pharmaceutically acceptable salts were prepared as pharmaceuticals, useful as antiinflammatories, immunosuppressants, and antiviral agents (no data). Mycophenolic acid was converted to its acid chloride and esterified with 4-morpholineethanol to give I [R = H, Y = (CH2CH2)2O, m = 2] which was then esterified with 1-adamantanecarbonyl chloride to give I.HCl [R = 1-adamantoyl, Y = (CH2CH2)2O, m = 2] (II). Tablets were prepared each containing II 400, cornstarch 50, lactose 145, and Mg stearate 5 mg.
IC ICM A61K031-535
ICS A61K031-55; C07D295-14
INCL 514211000
CC 26-6 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 15, 28, 63
IT **622-40-2**, 4-Morpholine ethanol
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(esterification of, by mycophenolic acid chloride)
IT **128794-94-5P**
RL: RCT (Reactant); **SPN (Synthetic preparation)**; **PREP (Preparation)**; RACT (Reactant or reagent)
(preparation and esterification of, by adamantoyl chloride)
IT **622-40-2**, 4-Morpholine ethanol
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(esterification of, by mycophenolic acid chloride)
RN 622-40-2 CAPLUS
CN 4-Morpholineethanol (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



IT **128794-94-5P**

RL: RCT (Reactant); **SPN (Synthetic preparation)**; **PREP (Preparation)**; RACT (Reactant or reagent)
(preparation and esterification of, by adamantoyl chloride)
RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



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'HITIND' IS NOT A VALID FORMAT FOR FILE 'USPATFULL'

The following are valid formats:

The default display format is STD.

ABS -------- AB
ALL -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD, RLI, PRAI, DT, FS, REP, REN, EXNAM, LREP, CLMN, ECL, DRWN, AB, GOVI, PARN, SUMM, DRWD, DETD, CLM, INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS, EXF, ARTU
ALLG ------- ALL plus PAGE.DRAW
BIB -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD, RLI, PRAI, DT, FS, EXNAM, LREP, CLMN, ECL, DRWN, LN.CNT
BIB.EX ----- BIB for original and latest publication
BIBG ------- BIB plus PAGE.DRAW
BROWSE ----- See "HELP BROWSE" or "HELP DISPLAY BROWSE". BROWSE must entered on the same line as DISPLAY, e.g., D BROWSE.
CAS -------- OS, CC, SX, ST, IT
CBIB ------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PRAI, DT, FS
DALL ------- ALL, delimited for post-processing
FP --------- PI, TI, IN, INA, PA, PAA, PAT, PTERM, DCD, AI, RLI, PRAI, IC, ICM, ICS, INCL, INCLM, INCLS, NCL, NCLM, NCLS, EXF, REP, REN, ARTU, EXNAM, LREP, CLMN, DRWN, AB
FP.EX ------ FP for original and latest publication
FPALL ------ PI, TI, IN, INA, PA, PAA, PAT, PETRM, DCD, AI,

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            RLI, PRAI, IC, ICM, ICS, INCL, INCLM, INCLS, NCL, NCLM,
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            PARN, SUMM, DRWD, DETD, CLM
FPBIB ------ PI, TI, IN, INA, PA, PAA, PAT, PTERM, DCD, AI,
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FHITSTR ---- HIT RN, its text modification, its CA index name, and
            its structure diagram
FPG -------- FP plus PAGE.DRAW
GI --------- PN and page image numbers
HIT -------- All fields containing hit terms
HITRN ------ HIT RN and its text modification
HITSTR ----- HIT RN, its text modification, its CA index name, and
            its structure diagram
IABS ------- ABS, indented with text labels
IALL ------- ALL, indented with text labels
IALLG ------ IALL plus PAGE.DRAW
IBIB ------- BIB, indented with text labels
IBIB.EX ---- IBIB for original and latest publication
IBIBG ------ IBIB plus PAGE.DRAW
IMAX ------- MAX, indented with text labels
IMAX.EX ---- IMAX for original and latest publication
IND -------- INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS,
            EXF, ARTU, OS, CC, SX, ST, IT
ISTD ------- STD, indented with text labels
KWIC ------- All hit terms plus 20 words on either side
MAX -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD,
            RLI, PRAI, DT, FS, REP, REN, EXNAM, LREP, CLMN, ECL,
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OCC -------- List of display fields containing hit terms
SBIB ------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, RLI, PRAI,
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SCAN ------- AN, TI, NCL, NCLM, NCLS, IC, ICM, ICS (random display
            without answer number.  SCAN must be entered on the
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STD -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, RLI, PRAI,
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STD.EX ----- STD for original and latest publication
TRIAL ------ AN, TI, INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC,
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ENTER DISPLAY FORMAT (STD):ibib abs hitstr
YOU HAVE REQUESTED DATA FROM 1 ANSWERS - CONTINUE? Y/(N):y

L24  ANSWER 1 OF 1  USPATFULL on STN
ACCESSION NUMBER:        2004:216021  USPATFULL
TITLE:                   Process for making mycophenolate mofetil by
                         transesterification
INVENTOR(S):             Lee, Kwang-Chung, Taoyuan, TAIWAN, PROVINCE OF CHINA
                         Lin, Shu-Chuan, Su-Lin, TAIWAN, PROVINCE OF CHINA
                         Chiu, Ray-Hwa, Su-Lin, TAIWAN, PROVINCE OF CHINA

                              NUMBER         KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2004167130      A1   20040826
APPLICATION INFO.:       US 2003-750466     A1   20031229  (10)
```

	NUMBER	DATE
PRIORITY INFORMATION:	TW 2003-92103728	20030221
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Lee, Kwang-Chung, P. O. Box 55-846, Taipei, 104	
NUMBER OF CLAIMS:	5	
EXEMPLARY CLAIM:	1	
LINE COUNT:	172	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

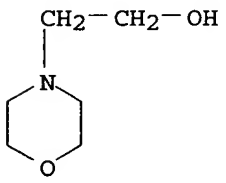
AB A process for making mycophenolate mofetil comprising: conducting a catalytic transesterification by reacting a low-carbon alkyl ester of mycophenolic acid with 2-morpholinoethanol [also named as 4-(2-hydroxyethyl) morpholine] to obtain a crude product of mycophenolate mofetil, which is then isolated and purified.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **622-40-2**, 4-(2-Hydroxyethyl)morpholine **31858-66-9**, Methyl mycophenolate **32483-51-5**, Ethyl mycophenolate **40336-78-5** **745067-13-4**
(process for preparation of mycophenolate mofetil by transesterification of mycophenolic acid esters with morpholinoethanol)

RN 622-40-2 USPATFULL

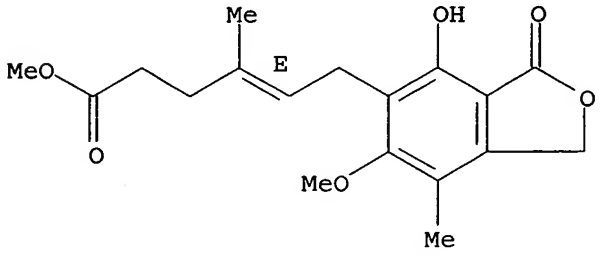
CN 4-Morpholineethanol (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



RN 31858-66-9 USPATFULL

CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, methyl ester, (4E)- (9CI) (CA INDEX NAME)

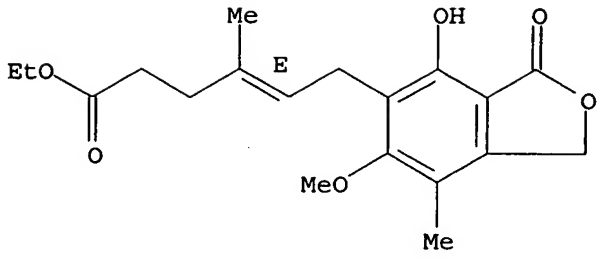
Double bond geometry as shown.



RN 32483-51-5 USPATFULL

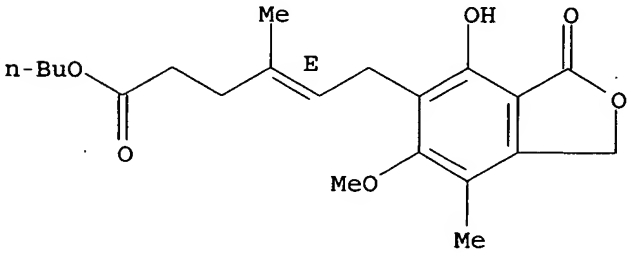
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



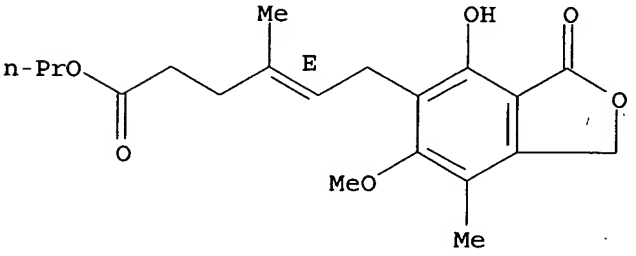
RN 40336-78-5 USPATFULL
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, butyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



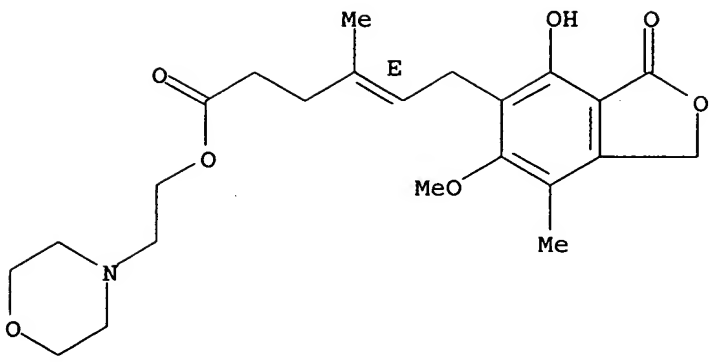
RN 745067-13-4 USPATFULL
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, propyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **128794-94-5P**, Mycophenolate mofetil
(process for preparation of mycophenolate mofetil by transesterification of mycophenolic acid esters with morpholinoethanol)
RN 128794-94-5 USPATFULL
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.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O
O
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